Orthopaedics & Traumatology: Surgery & Research (2013) 99, 645—651



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ORIGINAL ARTICLE

# Relation between nasal carriage of *Staphylococcus aureus* and surgical site infection in orthopedic surgery: The role of nasal contamination. A systematic literature review and meta-analysis

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Accepted: 28 March 2013

**KEYWORDS**
*Staphylococcus aureus*;
Nasal carriage;
Orthopedic surgery;
Meta-analysis;
Prevention;
Mupirocin

**Summary** *Staphylococcus aureus* is the pathogen most frequently implicated in infection on orthopedic hardware; various strategies are deployed to limit the risk of transmission and surgical infection.
*Objectives:* The present study is based on a meta-analysis assessing firstly the relationship between nasal carriage of *S. aureus* and the development of osteo-articular infection and secondly current methods of decolonization.
*Results:* The meta-analysis showed increased risk of surgical site infection in case of nasal carriage of *S. aureus*: OR = 5.92, 95% CI [1.15—30.39]; *P* = 0.033. For cross-transmission, a scientifically proven reduction in surgical site *S. aureus* levels is ensured by associated mupirocin and 2% chlorhexidine antiseptic solution in subjects with positive nasal screening results for all surgical procedures taken together; the reduction was not, however, significant in the orthopedic surgery subgroup. The meta-analysis confirmed these findings: OR = 0.60, 95% CI [0.34—1.06]; *P* = 0.08.
*Conclusion:* The literature review confirmed that nasal carriage of *S. aureus* is a major risk factor for surgical site infection. The efficacy of eradication could not be demonstrated for

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1877-0568/$ - see front matter 
http://dx.doi.org/10.1016/j.otsr.2013.03.030

orthopedic surgery as samples were too small. The positive trend found, however, should encourage further studies with sufficient power and risk/benefit should meanwhile be assessed on a case-by-case basis.
*Level of evidence:* Level 2. Meta-analysis.


## Introduction

Infection on material is one of the most frequent complications in orthopedic surgery. The number of orthopedic implantation procedures in France in 2009 was estimated by the PMSI information system at 229,171, with 125,340 hip replacements, 71,122 knee replacements, 9320 shoulder replacements and 23,389 revision procedures. Systematic perioperative antibioprophylaxis and theater air filtration by laminar flow or ceiling ventilation would seem to have reduced peroperative infection rates. The most recent ISO-RAISIN survey of 838 health establishments in 2008 reported 1.26% incidence of surgical site infection (SSI) [1]. A retrospective study of femoral neck fractures conducted by an antibioprophylaxis research group for the first quarter of 2005 reported an SSI rate of 5.6% at 1 year's follow-up [2]; *Staphylococcus aureus* was the most frequent pathogen (37%) implicated in post-surgical infections. Traditionally, prevention of *S. aureus* infection is founded on controlling cross-transmission: i.e., from patient to patient and environment to patient (usually via the care-team's hands); this can be called ''hand-carriage prevention''.

The literature reports three strategies of *S. aureus* SSI prevention: screening for and isolating methicillin-resistant *S. aureus* (MRSA) carriers; vancomycin antibioprophylaxis in patients at risk of MRSA; and local decontamination [3]. However, 80% of nosocomial *S. aureus* infections come from the patient's own flora [4]. Longitudinal studies reported that about 20% of the population are permanent and 30% intermittent *S. aureus* carriers [5]. There are several types of colonization site, usually associated but sometimes isolated. Isolated nasal carriage is estimated at 15.6%, isolated pharyngeal carriage at12.4% and the association at 20.8% [6]. Nasal carriage is a frequently reported risk factor [7—12] and many studies have demonstrated the efficacy of mupirocin in carriage eradication [13—21].

However, two questions remain: is there a correlation between nasal *S. aureus* carriage and osteo-articular infection; and what methods of decolonization exist and with what efficacy?

## Method

To address these questions, a literature review was conducted with the inclusion criteria and strategy outlined below.

### Inclusion criteria

Using the French Health Authority (HAS) levels of evidence (ANAES 2000 guidelines for literature analysis and recommendations grading), prospective randomized studies (level of evidence 1) were selected in priority, and supplemented by cohort studies, well-conducted non-randomized comparative studies or low-power randomized comparative studies (level of evidence 2), case-control studies (level of evidence 3) and retrospective studies, comparative studies with significant bias or case series (level of evidence 4), assessing prevention of *S. aureus* infection following orthopedic surgery in nasal *S. aureus* carriers, regardless of gender and age. Recommendation grades were classified according to the above guidelines as: grade A, established scientific proof (level of evidence 1); grade B, presumptive scientific demonstration (level of evidence 2); grade C, low level of evidence (levels of evidence 3 or 4).

Studies in which nasal carriage was detected either by cell culture or by genomic amplification were candidates for inclusion.

Results were required to distinguish carriers and non-carriers of *S. aureus*. When preventive treatment was administered before surgery, the control group could either receive placebo or no treatment.

The principle assessment criterion was percentage methicillin susceptible or resistant SSI, according to the Centers for Disease Control and Prevention (CDC) criteria [7].

### Search strategy

The search of the literature applied key-words to the Cochrane Central Register of Controlled Trials (latest version), EMBASE and MEDLINE (up to January 2011).

To seek answers to the questions of the relationship between nasal carriage and risk of postoperative *S. aureus* osteo-articular infection and of the various decolonization methods and their relative efficacy, the following key-words were entered, alone or combined:

- ''nasal carriage *S. aureus*'';
- and ''orthopedic or bone surgery'';
- and ''nasal carriage *S. aureus* and mupirocin'';
- or ''*S. aureus* and surgical site infection and mupirocin'';
- or ''*S. aureus* and surgical site infection and chlorhexidine'';
- or ''nasal carriage *S. aureus* and decontamination''.

Selection was duplicated (PYL, MD) and discordances were discussed.

### Statistical analysis

Results were presented using the forest plot option of the Comprehensive Meta-analysis package (Biostat). Percentage

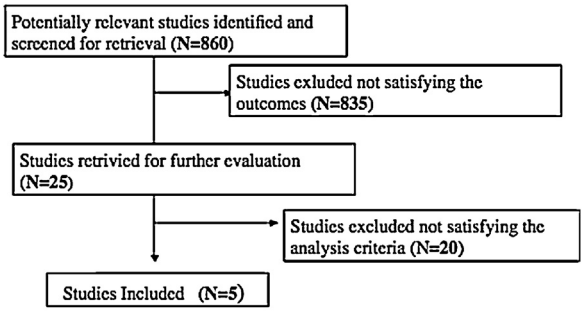


**Figure 1** Effect of nasal carriage: selection procedure for studies meeting the inclusion criteria.

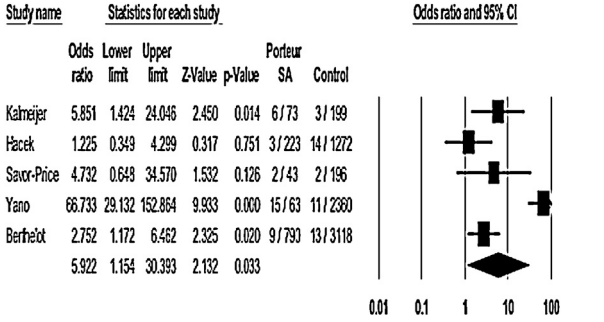


**Figure 2** Effect of nasal *Staphylococcus aureus* carriage on surgical site infection. Point forest display. The last line corresponds to the summary effect on the random effects model: OR = 5.92, 95% CI [1.15—30.39]; $P = 0.03$.

*S. aureus* infection was expressed as relative risk (RR) with 95% confidence intervals. Results from different studies were compiled on the random effects model, as they were not based on the same methodology. Heterogeneity was analyzed on $Chi^2$, with a significance threshold of $P = 0.05$. $I^2 > 50\%$ indicated significant heterogeneity between studies.

## Results

### Is there a relationship between nasal *S. aureus* carriage and the development of osteo-articular infection?

An initial search using ''nasal carriage *S. aureus*'' retrieved 860 references, reduced to 25 by crossing with ''*orthopedic or bone surgery*'' (Fig. 1). A total of five studies in orthopedic surgery were selected; the other 20 were excluded either because they did not concern joint surgery or because they failed to provide carrier data:

- Kalmeijer et al. [8] (Level of evidence: 2) demonstrated in 2000 that the sole independent risk factor for postoperative *S. aureus* infection was significant nasal *S. aureus* carriage ($P = 0.002$). Semi-quantitative screening was performed in a cohort of 272 patients admitted for implantation: 27% screened positive (10% weakly); 18/272 (6.6%) developed SSI, including nine implicating *S. aureus*, six of whom had screened positive;
- Hacek et al. [9] (Level of evidence: 3) assessed a detection and decolonization program in a non-randomized study of 912 patients and 583 controls. 223 of the 912 patients followed up at 2—4 weeks postoperatively screened positive and received mupirocin twice daily for 5 days up to the eve or morning of surgery: three developed SSI; four of the 689 negative patients developed infection. Ten of the 583 control subjects (416 from a historic group and 167 concomitantly admitted but not involved in the program) developed infection. The screening and decolonization program obtained a significant reduction in SSI at 1 year in patients who screened positive and underwent decolonization ($P < 0.05$; 95% CI = 2.2—10); in the 192 patients taken as a whole, carriers and non-carriers, there was no significant reduction ($P < 0.1\%$);
- Price et al. [10] (Level of evidence: 2) analyzed preoperative nasal carriage in orthopedic surgery. Eighty-six out of 284 patients were *S. aureus* carriers, including five with MRSA. Four of the 284 developed SSI: zero of the 43 decolonized by mupirocin, two carriers who had refused decolonization, and two of the 196 non-carriers. Sample sizes were too small to demonstrate significance;
- Yano et al. [11] (Level of evidence: 2) studied the relation between pre-existent nasal MRSA carriage and MRSA ISS in a cohort of 2423 orthopedic in-patients followed up for 26 months: incidence differed between carriers and non-carriers (4/63 vs. 11/2,360, respectively; $P = 0.001$);
- Berthelot et al. [12] (Level of evidence: 2) performed a multicenter study, including 3908 patients. *S. aureus* was detected pre-operatively in 790 (20%) patients. There were 77 cases of SSI, 22 of which implicated *S. aureus*. Nine of the 77 cases were carriers, although only in six was the strain the one that was detected preoperatively. The study involved a methodological limitation, as in half of the nine cases (5/9), strains were compared by phenotypic analysis of an antibiogram based on a single clone, whereas carriage may be multiclonal.

The present meta-analysis of these five studies focusing on osteo-articular infection (Fig. 2) found a significant impact of nasal *S. aureus* on *S. aureus* SSI: OR = 5.92, 95% CI [1.15—30.39]; $P = 0.033$. The random effects model was used, as heterogeneity was elevated: $I^2 = 90$; $P < 0.001$.

### What methods of decolonization are used, with what efficacy?

The initial search for ''nasal carriage *S. aureus*'' retrieved 860 references, reduced to 185 when crossed with ''*mupirocin*'', to 25 when crossed with ''*orthopedic or bone surgery*'' and to seven with all three key-words (Fig. 3). Six studies dedicated to orthopedic surgery were analyzed together; a study of nasal decontamination associated to antiseptic douche was analyzed separately.

#### Isolated nasal decontamination

We shall first present three systematic reviews of the literature [13—15] and one meta-analysis [16], which recently reported on mupirocin in postoperative *S. aureus* infection:

- Kallen et al. [13], analyzing three randomized trials and four cohort studies, found no reduction in SSI in general

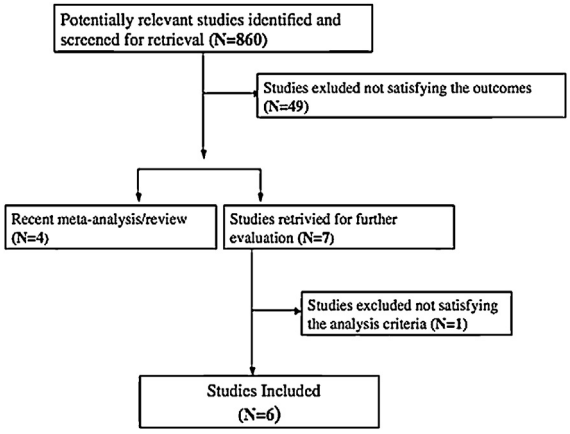


**Figure 3** Nasal decolonization. Selection procedure for studies meeting the inclusion criteria.

surgery, but a significant effect of mupirocin in specialized (cardiothoracic and orthopedic) surgery in the randomized studies. Only one randomized study [17] and one cohort study [18] specifically focused on orthopedic surgery;

- Trautman et al. [14], analyzing four randomized trials and seven cohort studies of nasal decontamination versus placebo or no treatment in SSI prophylaxis in elective surgery, found no reduction in *S. aureus* SSI with mupirocin in orthopedic, digestive or cardiac surgery. Only one randomized study [17] and two cohort studies [18,19] specifically focused on orthopedic surgery;
- These reviews mixed together results for systematic treatment of all patients and targeted treatment. In contrast, Van Rijen et al. [15] (Level of evidence: 1) analyzed mupirocin efficacy specifically in patients screening positive for nasal *S. aureus*. There were four randomized trials, including 1 in orthopedic surgery [17]. Treatment duration, however, varied from 1 to 7 days, depending on the study. Mupirocin reduced the rate of nosocomial *S. aureus* infection as a whole (RR = 0.55, 95% CI [0.34—0.89]), but there was no significant difference for SSI in particular. The authors attributed this to lack of power: expected SSI rates in the placebo group greater than those observed, multifactor causes of SSI onset, and heterogeneous surgery population;
- The Cochrane Collaboration publishes a systematic review of mupirocin efficacy in the prevention of *S. aureus* infection. A meta-analysis by Van Rijen published in 2008 [16] (Level of evidence: 1) showed that, in nasal *S. aureus* carriers, mupirocin significantly reduced *S. aureus* infection (RR = 0.55, 95% CI [0.43—0.70]). There were nine randomized controlled trials, four of which concerned surgery patients (but only one for orthopedic surgery [17]). The surgery sub-group showed a significant reduction in nosocomial *S. aureus* infection with mupirocin (RR = 0.56, 95% CI [0.34—0.91]), but which failed to extend to SSI specifically (RR = 0.63, 95% CI [0.38—1.04]). The authors explain that this particular analysis was not planned for in the study design, whence a lack of power.

Of the six studies considered for the present meta-analysis, only one DBRPCT (double-blind randomized placebo controlled trial) [17] and an orthopedic surgery subgroup within a randomized double-blind trial, but associating mupirocin to chlorhexidine [20], met the selection criteria. Kalmeijer et al.'s DBRPCT [17] (Level of evidence: 1) included 614 patients scheduled for orthopedic implant surgery. Mupirocin and placebo were administered twice daily to 315 and 299 patients respectively at eve and morning of surgery. Possible SSI was investigated for 1 month's follow-up. Baseline colonization was 30% in the mupirocin group and 29% in the placebo group; 16% of positive samples (15/95) remained positive at 3 to 5 days in the mupirocin group, versus 71% (61/86) in the placebo group, demonstrating efficacy. However, no significant impact could be shown on SSI due to lack of power: there was a trend toward efficacy (12/315 [4%] vs. 14/299 [5%]), but the difference was not significant as the infection rate in the placebo group was lower than expected although higher than in the literature in general.

Two open but non-randomized studies in orthopedic surgery included *S. aureus* carriers and non-carriers, with historic control groups:

- Gernaat van der Sluis et al. [18] (Level of evidence: 2), comparing 1044 patients treated with mupirocin and 1,260 controls without treatment, found a significant reduction in SSI ($P = 0.02$);
- Wilcox [19] (Level of evidence: 4), did not report percentages, but claimed that SSI was unaffected by mupirocin; this study was excluded from analysis.

Since 2008, three non-randomized cohort studies of mupirocin have focused exclusively on orthopedic surgery.

- Rao et al. [20] (Level of evidence: 2), in a non-randomized study, compared 636 arthroplasty patients with screening and decolonization when positive and two control groups: one operated on 1 year before the study and the other without decolonization. In the study group, 164/636 (26%) screened positive and none showed SSI over 1 year's follow-up; 12 (3.5%; $P = 0.016$) of an estimated 346 carriers in a control population of 1330 (26%) had *S. aureus* infection;
- Hacek et al. [9] (Level of evidence: 3), in a non-randomized study, reported that a screening and decolonization program significantly reduced SSI in decolonized (i.e., *S. aureus* positive) patients ($P < 0.05$; 95% [2.2—10]);
- Savor Price et al. [10] (Level of evidence: 2) analyzed preoperative nasal carriage in 284 orthopedic surgery patients but, as previously noted, with insufficient power to demonstrate any difference.

### Nasal decolonization associated to antiseptic douche

The efficacy of whole-body chlorhexidine 4% douche against MRSA strains was reported in a double-blind randomized trial [21] (Level of evidence: 1). Intranasal mupirocin associated to chlorhexidine soap proved effective against MRSA carriage in patients under hemodialysis [22]. Efficacy was likewise demonstrated in SSI in a randomized study of carrier surgery patients. Bode et al. [23] (Level of evidence: 1) performed a randomized double-blind study of 6771 patients,

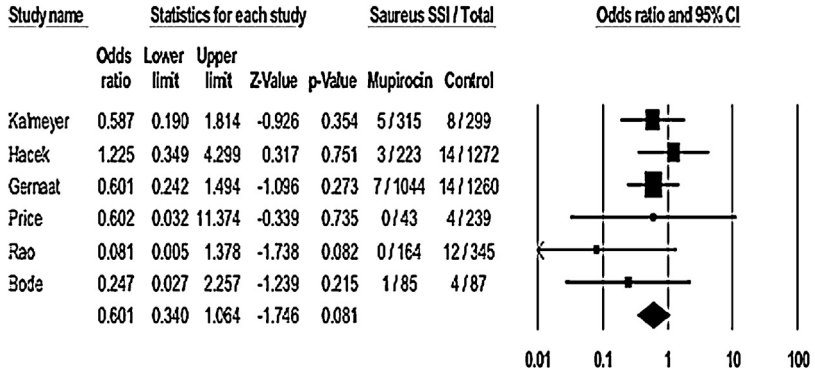


**Figure 4** Effect of mupirocine on *Staphylococcus aureus* surgical site infection. Point forest display. Mupirocin: group receiving pre-operative mupirocin. Control: no preventive treatment. The last line corresponds to the summary effect on the random effects model: OR = 0.60, 95% CI [0.34—1.06]; *P* = 0.08.

1251 of whom screened positive (18.8%). 913 were randomized: 505 with two local applications of mupirocin daily for 5 days and daily chlorhexidine antiseptic douche, versus 413 placebos. *S. aureus* infection was significantly lower in the treatment group (RR = 0.42, 95% CI [0.23—0.75]), and more especially in deep SSI (RR = 0.21, 95% CI [0.07—0.62]). The SSI ratio, however, was not reported. For the 172 orthopedic surgery patients, there was no significant difference between treatment and placebo groups (RR = 0.25, 95% CI [0.03—2.26]).

A meta-analysis of six studies (with full or partial study data) focusing specifically on osteo-articular infection (Fig. 4) found a trend for mupirocin to reduce *S. aureus* SSI: OR = 0.60, 95% CI [0.34—1.06]; *P* = 0.08.

### Choice of molecule

Mupirocin is the most frequently studied molecule for the eradication of nasal *S. aureus* carriage and its efficacy has been convincingly demonstrated in randomized double-blind trials [21—23] (All level of evidence 1). Another randomized double-blind trial showed it to be more effective than bacitracin [24] (Level of evidence: 1), and it proved more effective than Neomycin sulfate in a lower level study [25] (Level of evidence: 3). Comparable results were found in an open trial against an association of topical fusidic acid and oral trimethoprim—sulfamethoxazole [26] (Level of evidence: 2). A recent randomized double-blind trial comparing Polysporin Triple (PT: polymixin B, bacitracin, gramicidin) versus mupirocin found PT to be less effective at 12 weeks in eradicating MRSA [27] (Level of evidence: 1). Batumin ointment was studied in 56 healthcare staff in Ukraine [28] (Level of evidence: 3), and found to be more effective than mupirocin or associated bacitracin-Neomycin; this was, however, an isolated study.

The choice of antiseptic is important: a randomized double-blind trial found 2% alcoholic chlorhexidine to be significantly more effective than iodized povidone in preventing superficial (*P* = 0.008) and deep (fascia, muscles: *P* = 0.05) SSI [29] (Level of evidence: 1). Likewise, a recent meta-analysis of blood-culture contamination prevention showed alcoholic chlorhexidine to be more effective than aqueous iodized povidone (RR: 0.33, 95% CI [0.24—0.46]) [30]; however, chlorhexidine concentration varies with the excipient (4% soap, 2% alcohol).

## Discussion

The literature review was intended to address two questions: is there a relation between nasal *S. aureus* carriage and onset of osteo-articular infection? And what decolonization methods exist and what is their efficacy, notably as regards the association of local mupirocin and chlorhexidine (or other disinfectant) douche?

Nasal carriage is a well-established risk factor for infection in patients undergoing surgery or dialysis, intravascular device bearers, liver cirrhosis patients and those in intensive care [31]. A very recent genetic association study using multilocus sequence typing and identification of hypervariable gene regions coding for clumping factor and fibronectin demonstrated a strong relationship between asymptomatic nasal carriage strains and those found in clinical samples [32]. Munoz et al. [33] determined independent risk factors for infection after cardiac surgery: multivariate analysis identified nasal *S. aureus* carriage (RR = 3.1), re-do surgery and diabetes. The present meta-analysis, based on a single randomized study and some non-randomized studies in orthopedic surgery confirmed this risk; the levels of evidence allow a strong scientific presumption of correlation between *S. aureus* carriage and *S. aureus* SSI (grade B recommendation). Many reports confirm the high efficacy of mupirocin versus placebo in eradication of nasal *S. aureus* carriage over the short term, which is quite long enough for the purposes of SSI prevention [13—21]; where long-term treatment is indicated, however, mupirocin fails to ensure eradication and the risk of developing resistance is increased.

The efficacy of mupirocin in infection prevention by carriage eradication has been clearly demonstrated, with a significant reduction in *S. aureus* infection in general. The meta-analysis, however, failed to demonstrate reduction for SSI in particular, probably due to lack of statistical power.

In all, the levels of evidence of the above studies support the following conclusions:

- there is established scientific evidence (grade A recommendation) that mupirocin is more effective than other agents in eradicating nasal *S. aureus* carriage [23—34];
- there is established scientific evidence (grade A recommendation) that 2% alcoholic chlorhexidine is more effective than aqueous iodized povidone in preventing superficial and deep infection [21,22];
- there is no established scientific evidence that mupirocin alone reduces the risk of orthopedic *S. aureus* SSI [17,18]: the cited studies report a sub-significant trend;
- there is, on the other hand, established scientific evidence (grade A recommendation) for a significant reduction in *S. aureus* SSI with associated mupirocin and 2% chlorhexidine antiseptic solution in case of positive nasal screening, but this significant reduction fails to hold for the orthopedic surgery subgroup [23].

The present meta-analysis of the above studies confirmed this sub-significant trend toward efficacy. Several explanations may be given for the failure to demonstrate significance. Firstly, a very high number of patients is statistically required in each arm, as the prevalence of postoperative infection in orthopedic surgery is less than 1%. Secondly, non-nasal, and notably pharyngeal, infection sites [6,35] also cause contamination, but decontaminating them is more difficult and seldom attempted. Nasal carriage by staff is known to be an external source of contamination [36,37] and may also be a source of bias: recent studies have shown that staff decontamination by mupirocin reduced the rate of patient infection in orthopedic surgery [38]. It may also sometimes be difficult to implement patient decontamination protocols, given the diagnosis time (2 days per culture) and treatment duration (3 days, but varying up to 7 days according to the study): decontamination may thus be too late or impossible with respect to surgery, especially in traumatology or emergency settings. Finally, failure to distinguish carriers and non-carriers will have reduced the observed efficacy of mupirocin in certain of the studies.

## Conclusion

Nasal carriage is a major risk factor for orthopedic surgical site infection. Given the proven efficacy of associating local mupirocine for 5 days before surgery to 2% chlorhexidine douche in preventing *S. aureus* infection (grade A recommendation), even though this was reduced to a mere trend in the results restricted to orthopedic surgery because of a shortage of randomized studies, the benefit of this association on patients who screen positive should be considered on a case by case basis. In surgery that is urgent or scheduled within 6 days, systematic mupirocin with no screening or relying on rapid molecular biology tests is worth investigating.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

*Funding:* the present study was financed by the Direction Générale de la Santé (health authority) (open tender MA 1000996, dated December 24, 2010).

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## Further reading

**Selected articles not meeting criteria**

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